IN THE UNI. D STATES PATENT AND TRADEMARK OFFICE

Applicants:	Elazar Rabbani et al.
Serial No.	08/978,636
Filed:	November 25, 1997
Title:	NON-NATIVE POLYMERASE ENCODING NUCLEIC ACID CONSTRUCT (As Previously Amended)

Group Art Unit: 1635

Examiner: Mary M. Schmidt

527 Madison Avenue, 9th Floor
New York, New York 10022
August 18, 1999

Honorable Commissioner
of Patents and Trademarks
Washington, D.C. 20231

DECLARATION UNDER 37 C.F.R. §1.821(g)

Dear Sirs:

RONALD C. FEDUS hereby declares as follows:

1. I am the attorney in charge of the above-identified application, and I am fully familiar with its content.

2. I have compared the information transmitted via seq id nos: 1-51 as per the paper copy submitted with the accompanying Communication, and attest that they present no new matter.

3. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of title 18 of the United States code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

August 18, 1999
Date

Ronald C. Fedus
Registration No. 32,567
Attorney for Applicants

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FIRST CLASS CERTIFICATE

I hereby certify that this correspondence is being deposited today with the U.S. Postal Service as first class mail in an envelope addressed to Commissioner of Patents & Trademarks Washington, D.C. 20231

AUG 18 99
Date

Ronald C. Fedus
Reg. No. 32,567

4. X The Commissioner is hereby authorized to charge payment of the filing fee as well as the following fees associated with this application or to credit any overpayment to Deposit Account No. 05-1135. A **duplicate** copy of this sheet is enclosed.

X Any additional filing fees required under 37 CFR §1.16.

X Any patent application processing fees under 37 CFR §1.17.

5. X The Commissioner is hereby authorized to charge payment of the following fees during the pendency of this application or credit any overpayment to Deposit Account No. 05-1135. A **duplicate** copy of this sheet is enclosed.

X Any patent application processing fees under 37 CFR §1.17.
___ The issue fee set in 37 CFR §1.18 at or before mailing of the Notice of Allowance, pursuant to 37 CFR §1.311(b).
___ Any filing fees under 37 CFR §1.16 for presentation of extra claims.

6. ___ A check in the amount of $_____ is enclosed.

7. ___ Cancel claims _____.

8. X Amend the specification by inserting before the first line of the sentence: ----This is a X continuation, ___ divisional, ___ continuation-in-part, of application Serial No. 08/978,636, filed on November 25, 1997.---

9. X Transfer the drawings from the prior application.

10. ___ Informal ___ Formal ___ drawings are enclosed.

11. ___ Abandon said prior application as of the filing date accorded this application. A **duplicate** copy of this sheet is enclosed for filing in the prior application file.

12. ___ Priority of application Serial No. _____ filed on _____ is claimed under 35 U.S.C. §119. The certified copy of the priority application has been filed in prior application Serial No. _____, filed _____.

13. ___ The prior application is assigned of record to Enzo Therapeutics, Inc., c/o Enzo Biochem, Inc., 527 Madison Avenue, New York, New York 10022. [A copy of the originally submitted Assignment and the Notice of Recordation are enclosed herewith.]

14. ___ A preliminary amendment is enclosed.

15. X The power of attorney in the prior application is to: Ronald C. Fedus, Reg. No. 32,567.

(a) X The power appears in the original papers in the prior application.

(b) _____ Since the power does not appear in the original papers, a copy of the power in the prior application is enclosed.

(c) _____ A copy of a new substitute power of attorney is enclosed.

(d) X Address all future communications to: (May only be completed by applicant, or attorney or agent of record.)

Ronald C. Fedus, Esq.
Enzo Therapeutics, Inc.
c/o Enzo Biochem, Inc.
527 Madison Avenue (9th Floor)
New York, New York 10022

16. _____ I hereby verify that the attached papers are a true copy of prior application Serial No. _____.

The undersigned declares further that all statements made herein of his own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

May 10, 2000
Date

Ronald C. Fedus
Registration No. 32, 567
Attorney for Applicants
_____ Inventor(s)
_____ Assignee of Complete Interest
X Attorney or Agent of Record
_____ Filed under 37 CFR §1.34(a)

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Furthermore, plasmids are taught containing anti-sense segments introduced into the transcript region of the U1 gene, plasniid pHSD-4 U1 so that upon expression of the transcript, the antisense RNA sequence is produced to the complementary region of the HIV genome. Specifically, pDU1-A, B, C and D were made using the antisense A, B, and C sequences previously described and D as a control containing a non-HIV sequence. A multi-cassette version of the constructs was also made by sub-cloning in tandem the A,B, and C antisense to make pNDU1 (A,B,C) (N meaning the construct was also contained the gene for neomycin resistance).

Other multi-cassette constructs taught were:

(1) TRI 101, an M13 phage vector containing the "A" antisense T7 operon , the "B" antisense T7 operon and the "C" antisense T7 operon in a single construct (figure 46). Co-transfection would be required for expression of the antisense molecules from this construct with a vector that expresses T7 RNA polymerase (suggested is the intron containing construct of example 19); and,

(2) an M13 construct constructed from a multi-ligation of portions of plNT-3 (containing the intron containing polymerase) and the T7 promoter driven A, B, and C sequences (see figure 47).

The specification teaches application of some of these constructs ("various U1 constructs described above" p. 167, last line) in antisense inhibition of HIV in infected U937 cell culture. Specifically the following is shown: (1) expression of A, B, and C antisense by hybridization analysis after expression of the "U1 clone" (p. 169, line 3), (2) expression of the "triple U1 construct" (p. 169, para. (c), line 1) which result in a decrease in p24 production next to the control, and increased % reduction in p24 over time and after re-infection of cells, and these results were confirmed by absence p24 amplification next to control cells via PCR of the targeted DNA, and (3) expression of the construct of figure 50, a fusion product antisense A upstream of B-gal gene where antisense activity of the A portion caused inhibition of B-gal activity as shown in lacZ assays. The results in figure 51 show HIV A/Anti-A activity and HIV A/Anti-ABC (when the triple U1 construct was used by *co-transfection)* as the equivalent of the uninfected cells whereas the infected and control containing cells showed high B-gal expression. Therefore, it does not appear in the specification as filed that the multicassette A,B,C and T7 polymerase construct (expressed on same plasmid) was applied to the same HIV challenge experiments.

Additional constructs are more prophetically taught: the primary nucleic acid construct that propagates production centers for the production of single-stranded antisense, etc. in examples 21-25, and the retrovirus vector containing sequences for the expression of antisense RNA directed at HIV on page 181, last para.

Further comments by the Examiner continued on pages 9-11:

Claims 22-24 read on any construct bound non-ionically to a ligand or otherwise chemically modified entity, further limited as having a polynucleotide tail terminus and where the tail is hybridized to

a complementary polynucleotide sequence. The breadth of genus sought for such is not enabled in view of the lack of specificity of guidance in the specification as filed. The specification fails to provide guidance for the breadth claimed since the claims vaguely claim "constructs" which "produce products." The specification teaches only by way of example HIV inhibition by antisense expression from vector constructs which do not entail chemical modified entities nor polynucleotide termini.

Claims 255-260 are further broadly drawn to a nucleic acid construct for producing a product in a cell which includes a "processing element" that is "substantially removed during processing" in a "compatible cell." The language "processing element" reads on expression of any gene from said construct that has a "processing" function in a cell, for example, any ribozyme, polymerase, or any protein causing a modification of any molecule (protein or DNA)in a cell. The scope of the genus sought for such constructs is not enabled in view of the lack of specificity of guidance in the specification as filed. The specification fails to provide guidance for the breadth claimed since the claims nebulously claim "constructs" which produce "products" having a "processing" function. The specification teaches only prophetically an intron containing polymerase wherein the intron is removed in a compatible cell. The specification does not exemplify
application of the T7 polymerase/U1-A,B,C vector as described in example 19 in cells. It appears that only the U1A,B,C clone co-expressed with T7 polymerase (on another vector) is exemplified in the HIV challenge and LacZ assays.

Furthermore, the claims specify the context for producing the product in a cell and no exemplification of whole organism success is found in the specification as filed. There is a high level of unpredictability in the antisense art and analogous gene therapy art for *in vivo* (whole organism) applications. The factors considered barriers to successful delivery of antisense delivery to the organism are: (1) penetration of the plasma membrane of the target cells to reach the target site in the cytoplasm or nucleus, (2) withstanding enzymatic degradation, and (3) the ability to find and bind the target site and simultaneously avoid non-specific binding (see Branch). Despite the synthesis of more resilient, nuclease resistant, oligonucleotide backbones and isolated successes with antisense therapy *in vivo,* the majority of designed antisense molecules still face the challenge of successful entry and localization to the intended target and further such that antisense and other effects can routinely be obtained. Note Flanagan et al. who teach "although numerous reports have cited antisense effects using oligonucleotides added to cell medium, direct proof that oligonucleotides enter cells and affect gene inhibition by an antisense mechanism is still lacking (page48, column 1)."

Specifically, *in vitro* results with one antisense molecule are not predictive of *in vivo* (whole organism) success. *In vitro,* antisense specificity to its target may be manipulated by "raising the temperature or changing the ionic strength, manipulations that are commonly used to reduce background binding in nucleic acid hybridization experiments." (Branch, p. 48) Discovery of antisense molecules with "enhanced specificity" *in vivo* requires further

> experimentation for which no guidance is taught in the specification. Note Branch who teaches the state of the art for designing an antisense which inhibits a target *in vivo:* it "is very difficult to predict what portions of an RNA molecule will be accessible *in vivo,* effective antisense molecules must be found empirically by screening a large number of candidates for their ability to act inside cells (Branch, p.49)." And in the instant case, the claims read broadly on administration of an antisense inhibitor in any cell, therefore the whole organism included. While the specification teaches cell culture inhibition, no evidence of successful *in vivo* (whole organism) antisense inhibition has been shown, nor do the culture examples correlate with whole organism delivery.

The Examiner concluded her remarks on enablement on pages 11-12 where she stated:

> One of skill in the art would not accept on its face the successful delivery of the disclosed antisense molecules *in vivo* in view of the lack of guidance in the specification and the unpredictability in the art. Specifically the specification does not teach (1) stability of the antisense molecule *in vivo,* (2)effective delivery to the whole organism and specificity to the target tissues, (3) dosage and toxicity, nor (4) entry of molecule into cell and effective action therein marked by visualization of the desired treatment effects. These key factors are those found to be highly unpredictable in the art as discussed *supra.* The lack of teaching of these factors in the specification as filed, coupled to the amount of "trial and error" experimentation involved in the deduction of such results would lead one skilled in the art to necessarily practice an undue amount of experimentation for whole organism use of the claimed constructs.
>
> No determination of enablement can be made for claims 2-21 because there is no independent claim from which they depend. Without knowing what claims 2-21 depend on, the full scope of the claims is not known.

The enablement rejection is respectfully traversed.

With respect to the application of the enablement rejection to claims 2-24, such grounds have been rendered moot, of course, by the cancelation of these hereinabove.

With respect to claims 245-260, it is respectfully submitted that the subject matter of these claims is fully enabling such that a person skilled in the art could practice, without undue experimentation, Applicants' claimed invention. It is respectfully submitted that the ordinarily skilled artisan, armed with the disclosure,

could practice their non-native polymerase encoding nucleic acid construct and their nucleic acid construct that produces a nucleic acid product comprising a non-native processing element, as set forth in the present claims.

Reconsideration and withdrawal of the enablement rejection are respectfully requested.

The Rejection Under 35 U.S.C. §112, First Paragraph

Claims 2-24 and 245-260 stand rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. In the Office Action (pages 12-14), the Examiner stated:

> Claims 2-21 are drawn to a missing independent claim and therefore the scope claimed is not able to be determined. Claims 22-24 are drawn to a broad scope of constructs which are bound non-ionically to an entity having a chemical modification or a ligand and produce a product in a cell. Claims 255-260 are further broadly drawn to a nucleic acid construct for producing, a product in a cell which includes a "processing element" that is "substantially removed during processing" in a "compatible cell."
>
> The claims broadly encompass "constructs" for producing a "product" and it is not clear what is embraced by the claims. The claims read on vectors, genomes, cell processes like translation, transcription, etc. Furthermore, the scope of "chemical modification" as used in claim 22 is not clear in relation to the construct.
>
> The instant specification describes prophetically a number of potential modified nucleic acid constructs for expression of an entity in a cell. The supporting figures provide limited additional disclosure of relevant identifying structural characteristics because they primarily correspond to expression vector based constructs which are only one facet of the invention in light of the nebulous scope claimed.
>
> Clearly the specification only considers vector-like constructs for delivery and expression of nucleic acids. Specifically, for claims 255-260, use of processing elements other than the SV40 intron are not taught in a whole construct for subsequent functional use of production of nucleic acid products in claim 259 or protein binding nucleic acid sequences of claim 260.
>
> Furthermore, the actual constructs used in the HIV challenge and Lac-Z assays taught in the specification are not described in clear and exact terms (p. 169, line 3 recites "U1 clone"; p. 169, para. ©

line 1 recites "triple U1 construct" and p. 167, last line recites "various U1 constructs described above') and it is not clear whether the constructs used had the intron sequence **in** the T7 polymerase, or even which constructs were used in the assays.

Despite the known predictability of standard vector construction in the molecular biology art, in view of the nearly infinite scope claimed and the lack of adequate description in the specification for such a broad genus of possible "constructs," coupled with the high level of unpredictability for constructs which could fall within this genus such as those involving gene therapy, the specification as filed fails to provide one skilled in the art enough description to show possession of a representative number of "construct" species for the breadth claimed.

See the June 15, 1998 (Vol. 63, No. 114, Pages 32639-32645) Federal Register for the interim guidelines for the examination of patent applications under the 35 U S.C. 112 "Written Description" requirement.

The written description rejection is respectfully traversed.

With respect to claims 2-24, the cancelation of those claims above renders the instant description rejection moot as it applies to the now canceled claims.

With respect to claims 245-260, it is believed that the scope of these claims is of proper breadth and scope so as to reasonably convey to one skilled in the relevant art that the present inventors had possession at the time this application was first filed in December 1995 of the same matter now being claimed.

Reconsideration and withdrawal of the written description rejection are respectfully requested.

The First Rejection Under 35 U.S.C. §102

Claims 245-249, and 253 stand rejected under 35 U.S.C. §102(e) as being anticipated by Saito et al., U.S. Patent No. 5,610,067, issued on March 11, 1887, based upon an application filed on December 12, 1991. In the Office Action (page 15), the Examiner stated:

> The claimed invention is drawn to a nucleic acid construct for co-expression of a non-native polymerase causing expression of

another nucleic acid sequence in a cell. Further limitations include use of a tRNA primer and reverse transcriptase.

Saito et al. teach a vector for expression of retroviral genes in a cell, including expression of reverse transcriptase for production of genes associated with the action of the reverse transcriptase from a tRNA primer.

The rejection for anticipation by Saito et al. is respectfully traversed.

In response, Applicants respectfully contend that Saito's patent disclosure neither teaches nor suggests their claimed invention.

Reconsideration and withdrawal of this anticipation rejection is respectfully traversed.

The Second Rejection Under 35 U.S.C. §102

Claims 245-247, and 249-254 are rejected under 35 U.S.C. §102(e) as being anticipated by Wagner et al., 5,591,601, issued on January 7, 1997, based upon an application filed on May 14, 1993. In the Office Action (pages 15-16), the Examiner stated:

> The claimed invention is drawn to a nucleic acid construct for co-expression of a non-native polymerase causing expression of another nucleic acid sequence in a cell. Further limitations include use of a bacteriophage polymerase such as T3, T7 or SP6 and antisense DNA or RNA as the co-expressed nucleic acid sequence.
>
> Wagner et al. teach a vector construct for co-expression of an RNA polymerase (ex. T3, T7 or SP6, see col.8 line l 1) with a gene of interest (for example, antisense, ribozyme or any other gene the scope of which would include a nucleic acid sequence coding for a decoy to a viral protein) for enhancement of gene expression in cells. It is further within the scope of the invention to select a gene encoding an intron or a capping element for a polyadenylation signal.
>
> The rejection for anticipation by Wagner et al. is respectfully traversed.

In response, Applicants respectfully contend that there is a lack of identity of material elements between their claimed invention and Wagner's patent disclosure.

Reconsideration and withdrawal of this anticipation rejection is respectfully requested.

The Third Rejection Under 35 U.S.C. §102

Claims 22-24 stand rejected under 35 U.S.C. §102(e) as being anticipated by Meyer et al., U.S. Patent No. 5,574,142, issued on November 12, 1996, based upon an application filed on December 15, 1992. In the Office Action (page 14), the Examiner stated:

> The claimed invention is drawn to any construct which when present in a cell produces a product, and is bound non-ionically to an entity comprising a modification or a ligand, and further comprises a hybridized polynucleotide tail.
>
> Meyer et al. teach a covalently linked conjugate of an oligonucleotide (ODN) with a peptide and a carrier or targeting ligand (ODN-peptide-carrier) including a therapeutic oligonucleotide which is capable of selectively binding to a target sequence of DNA, RNA or protein inside a target cell. The invention of Meyer et al. Reads on all of the instant claimed limitations for a non-naturally occurring construct for production of a product in a cell (in Meyer, an antisense oligonucleotide is produced).

With the cancelation of claims 2-24 above, it is believed that the anticipation rejection based upon Meyer's patent has been rendered moot.

Reconsideration and withdrawal of this anticipation rejection are respectfully requested.

The Fourth Rejection Under 35 U.S.C. §102

Claims 255-260 are rejected under 35 U.S.C. §102(e) as being anticipated by Sullenger et al., U.S. Patent No. 5,854,038, issued on December 29, 1998, based upon an application filed on January 22, 1993. In the Office Action (pages 16-17), the Examiner stated:

> The claimed invention is drawn to a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non-native processing element, which when in a compatible cell, said processing element is substantially removed during processing. Further limitations include an RNA processing element (an intron or a polyadenylation signal and capping element), and the nucleic acid product being: single stranded, antisense DNA or RNA, sense DNA or RNA, a ribozyme or a protein binding sequence such as one that binds protein required for viral assembly or replication.
>
> Sullenger et al. teach expression of RNA-based inhibitors of viral replication by localization of an inhibitory RNA such as a ribozyme to the target. Ribozymes are known in the art to have a processing function and also have an inherent half-life and are therefore removed.

The anticipation rejection based on Sullenger is respectfully traversed.

Applicants respectfully contend that there is a lack of material identity between their claimed elements and Sullenger's disclosure.

Reconsideration and withdrawal of the rejection is respectfully requested.

The Fifth Rejection Under 35 U.S.C. §102

Claims 255-260 stand rejected under 35 U.S.C. §102(e) as being anticipated by Hurwitz et al., U.S. Patent No. 5,648,243, issued on July 15, 1997, based upon an application filed on July 31, 1991. In the Office Action (page 17), the Examiner stated:

> The claimed invention is drawn to a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non-native processing element, which when in a compatible cell, said processing element is substantially removed during processing. Further limitations include an RNA processing element (an intron or a polyadenylation signal and capping element), and the nucleic acid product being: single stranded, antisense DNA or RNA, sense DNA or RNA, a ribozyme or a protein binding sequence such as one that binds protein required for viral assembly or replication.
>
> Hurwitz et al. teach selective use of introns in an expressed gene for increased expression of the gene in a mammalian cell, specifically the product is human serum albumin.

The anticipation rejection by Hurwitz et al. is respectfully traversed.

It is respectfully contended that Hurwitz' patent neither discloses nor suggests Applicants' claimed invention. Reconsideration and withdrawal of this anticipation rejection is respectfully requested.

The Sixth Rejection Under 35 U.S.C. §102

Claims 255-260 stand rejected under 35 U.S.C. §102(b) as being anticipated by DeYoung et al. ["Functional Characterization of Ribozymes Expressed Using U1 and T7 Vectors for the Intracellular Cleavage of ANF mRNA," Biochemistry 33:12127-12138 (1994)]. In the Office Action (page 18), the Examiner stated:

> The claimed invention is drawn to a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non-native processing element, which when in a compatible cell, said processing element is substantially removed during processing. Further limitations include an RNA processing element (an intron or a polyadenylation signal and capping element), and the nucleic acid product being: single stranded, antisense DNA or RNA, sense DNA or RNA, a ribozyme or a protein binding sequence such as one that binds protein required for viral assembly or replication.
>
> DeYoung et al. teach expression of ribozymes imbedded in a U1 sequence and under the control of a T7 promoter. Ribozymes are known in the art to have a processing function and also have an inherent half-life and are therefore removed.

The anticipation rejection by DeYoung et al. is respectfully traversed.

It is believed that DeYoung's disclosure does not anticipate the present invention.

Reconsideration and withdrawal of the fourth anticipation rejection are respectfully requested.

The Rejection Under 35 U.S.C. §103

Claims 245-260 are rejected under 35 U. S.C. §103(a) as being unpatentable over DeYoung et al. as applied to claims 255-260 above in view of Karn et al. [U.S. Patent No. 5,821,046, issued on October 13, 1998, based upon an application filed on February 29, 1992], Wagner et al., Curiel et al. [U.S. Patent No. 5,547,932, issued on August 20, 1996] and Zaia et al. ["Status of Ribozyme and Antisense-Based Development Approaches for Anti-HIV-1 Therapy," Annals of the New York Academy of Sciences 660:12-15 (1992)]. In the Office Action (pages 19-22), the Examiner stated:

> Claims 245-254 are drawn to a nucleic acid construct for co-expression of a non-native polymerase causing expression of another nucleic acid sequence in a cell. Further limitations include use of a bacteriophage polymerase such as T3, T7 or SP6 and antisense DNA or RNA as the co-expressed nucleic acid sequence. Claims 255-260 are drawn to a nucleic acid construct which when introduced into a cell produces a nucleic acid product comprising a non-native processing element, which when in a compatible cell, said processing element is substantially removed during processing. Further limitations include an RNA processing element (an intron or a polyadenylation signal and capping element), and the nucleic acid product being: single stranded, antisense DNA or RNA, sense DNA or RNA, a ribozyme or a protein binding sequence such as one that binds protein required for viral assembly or replication.
>
> DeYoung et al. teach expression of ribozymes imbedded in a U1 sequence and under the control of a T7 promoter. DeYoung does not teach a cassette style expression of more than one sequence from the same vector, expression of specifically antisense to HIV tat/rev genes, nor co-expression of the T7 polymerase from the same vector.
>
> Wagner et al. teach a vector construct for co-expression of an RNA polymerase (ex. T3, T7 or SP6, see col. 8 line 11) with a gene of interest (for example, antisense, ribozyme or any other gene the scope of which would include a nucleic acid sequence coding for a decoy to a viral protein, see column 3) for enhancement of gene expression in cells. It is further within the scope of the invention to select a gene encoding an intron or a capping element for a polyadenylation signal. Wagner does not teach antisense expression to HIV in his claimed construct.
>
> Karn et al. teach antisense inhibition of the HIV TAT protein but does not teach co-expression of the antisense RNA with a T7 polymerase.
>
> Curiel et al. teach expression of tandem expression of "genetic units"(such as ribozyme or antisense sequences) "when it is simultaneously desired to produce inhibiting RNAs directed against various types of RNA." (See columns 27 and 28) Curiel also teaches

the idea of the size of the tandem "genetic units" as a limiting factor in the vector design.

Zaia et al. teach ribozymes as representing a "second generation" of antisense molecules for targeting HIV and teach the use of both synthetic antisense DNA and expressed antisense RNA for inhibition of HIV-1. (See page 101)

It would have been prima facie obvious at the time the invention was made for one of ordinary skill in the art to express in tandem antisense directed to HIV sequences from a phage vector containing U1 sequences flanking the antisense molecule (for fused expression and direction to the nucleus) under the control of a T7 promoter and subsequently to co-express the T7 polymerase on the same vector construct.

One of ordinary skill in the art would have been motivated to apply antisense to targets as demonstrated by Karn et al., one example from the art of antisense inhibition of HIV as a method of inhibition of viral proliferation. One of ordinary skill in the art would have been motivated to express the antisense sequences within U1 from a T7 promoter in the context taught by DeYoung for improved targeting of the antisense sequence to the nucleus. Although DeYoung teaches ribozyme placement in the U1 construct, it would have been obvious to exchange antisense nucleic acid sequences for ribozyme sequences, as Zaia teaches ribozymes are functional equivalents of expressed RNA antisense molecules. See further Wagner et at. who also taught expression of ribozymes or antisense equivalently from the same construct (column 3 and 7). One of ordinary skill in the art would have been motivated to express the antisense sequences on the same plasmid as T7 polymerase as taught by Wagner et al. to avoid co-transfection of the polymerase on a second vector for expression of the T7 promoter driven antisense in the mammallian cell. Further, one of ordinary skill in the art would have been motivated to express in tandem from said vector more than one U1-antisense sequence as taught by Curiel et al. for simultaneous application of antisense molecules to different targets.

One of ordinary skill in the art would have had a reasonable expectation of success to express an antisense sequence in place of the ribozyme sequence within a U1 sequence as in the construct taught by DeYoung et al. since Zaia et al. taught ribozymes and antisense were functional equivalents in the art. Wagner et al. further taught the interchangeability of ribozyme and antisense sequences for expression from a site on a vector (see column 7). One of ordinary skill in the art would have had a reasonable expectation of success to express U1-antisense "genetic units" in tandem (ie, with the associated desired transcriptional units surrounding each antisense sequence) as taught by Curiel with the number of possible units chosen limited only by the size and packaging constraints of the vector. Furthermore, one of ordinary skill in the art would have had a reasonable expectation of success to express a T7 polymerase on the same construct as the U1-antisense sequences as taught by Wagner et al.. Wagner taught the effective expression of the T7 polymerase and application of the expressed polymerase to further express antisense sequences (see column 3 and 7, lines 34-35) under control of a T7 promoter on the same vector construct in a mammallian cell.

Therefore, it would have been expected that the U1-antisense to HIV would have been expressed and sufficiently localized to the target region in the nucleus, and that application of known antisense molecules from the art would have resulted in the effective inhibition of the HIV target in any cell.

The obviousness rejection is respectfully traversed.

It is respectfully submitted that the differences between Applicants' claimed invention and the combined disclosures of the cited documents would not have been obvious to a person having ordinary skill of art at the time the present invention was made.

Reconsideration and withdrawal of the obviousness rejection is respectfully requested.

* * * * * * *

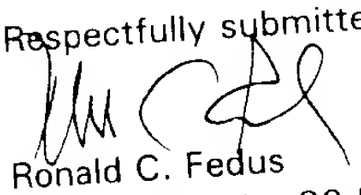
SUMMARY AND CONCLUSIONS

Claims 245-260 are being presented for further examination, with claims 2-24 having been canceled and claims 249, 251, 253, 257 and 259-260 having been amended above.

This Amendment is being accompanied by a Request For An Extension Of Time (3 months) and authorization for the small entity fee therefor. No other fee or fees are believed due for filing this Amendment. In the event that any other fee or fees are due, however, authorization is hereby given to charge the amount of any such other fee(s) to Deposit Account No. 05-1135, or to credit any overpayment thereto.

If a telephone conversation would further the prosecution of the present application, Applicants' undersigned attorney request that he be contacted at the number provided below.

Respectfully submitted,



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